◆CASE REPORT ◆

Drug-Eluting Balloon Angioplasty for Carotid In-Stent Restenosis

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Purpose: To report midterm results of 3 cases in which drug-eluting balloons (DEBs) were successfully used for the management of carotid in-stent restenosis (ISR).
Case Report: Two women aged 68 and 70 years and a 68-year-old man were referred to our institution for asymptomatic severe stenosis [>80% with peak systolic velocity (PSV) >300 cm/s by Doppler ultrasound assessment] of individual Carotid Wallstents implanted in the proximal left internal carotid artery (ICA). In the angiosuite, the left ICA was engaged in a telescopic fashion with a triple coaxial system formed by a 6-F long sheath and a preloaded 5-F, 125-cm diagnostic catheter over a 0.035-inch soft hydrophilic guidewire. Under distal filter protection, the lesions were predilated using a 3.5×20-mm coronary balloon and then treated with two 1-minute inflations of a 4×40-mm Amphirion In.Pact paclitaxel-eluting balloon, followed by 3 months of dual antiplatelet therapy. At 12, 22, and 36 months, respectively, the patients are still asymptomatic, with duplex-documented stent patency at 6, 12, and 24 months, respectively.
Conclusion: DEBs are an emerging strategy for carotid ISR, with encouraging midterm results in these patients. Further experience in larger cohorts is needed to confirm these preliminary observations.

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Key words: drug-eluting balloon, carotid stent, paclitaxel, stenosis, in-stent restenosis

Carotid artery stenting (CAS) is a valid alternative to carotid endarterectomy (CEA), particularly for high-risk patients,[1,2] with a comparable short-term outcome.[3] In-stent restenosis (ISR), however, is a possible complication of CAS, occurring in from 3% to 20% of cases, although symptom recurrence is relatively uncommon.[4]

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The ideal treatment for carotid ISR has yet to be defined. Re-stenting, repeat balloon (or cutting balloon) angioplasty, and surgical treatment have all been used, with variable results.[5] We report a case series in which the novel technology of drug-eluting balloons (DEB), widely used in the coronary circulation, was successfully applied to the management of carotid ISR.

CASE REPORT

Patient Histories

In July 2011, a 68-year-old woman was admitted to our department for asymptomatic

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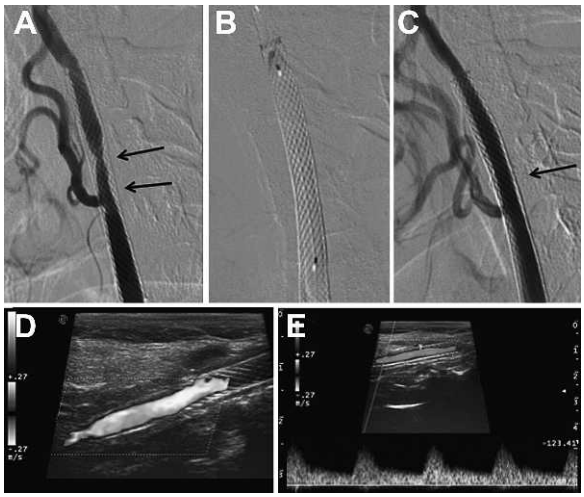

Figure 1 ◆ (**A**) Baseline digital subtraction angiogram of left internal carotid artery with evidence of multiple lesions and subocclusive restenosis (arrows). (**B**) Paclitaxel-eluting balloon dilation. (**C**) Completion angiogram showing optimal result at the restenosis site (arrow). (**D**, **E**) Six-month duplex ultrasound showing complete stent patency, with normal peak systolic velocity.

severe ISR (Fig. 1) of the left internal carotid artery (ICA) confirmed by duplex [>80% with peak systolic velocity (PSV) >300 cm/s]. She had undergone left CEA in December 2009, and a Carotid Wallstent (7×40 mm; Boston Scientific, Natick, MA, USA) was implanted in April 2010 for proximal subtotal reocclusion of the left ICA. Her history was significant for paclitaxel drug-eluting stents implanted in the right coronary and the left anterior descending arteries 3 years before due to acute coronary syndrome.

In the second case, a 70-year-old woman was referred to our institution in September 2010 for asymptomatic stenosis of a Carotid Wallstent (7×30-mm) that was implanted in the proximal left ICA in December 2009 followed by 1-month dual antiplatelet therapy. In August 2010, routine ultrasound examination of the supra-aortic trunks had shown severe in-stent restenosis (Fig. 2). She had a medical history significant for coronary artery disease (circumflex artery stenting in 2007) and peripheral vascular disease with known Leriche syndrome.

The last case involved a 68-year-old man admitted in July 2009 for asymptomatic severe left ICA stenosis of a Carotid Wallstent (7×30 mm) implanted the year before. He had a substantial history of vascular procedures, including bilateral common iliac artery stenting, surgical endarterectomy of the right common femoral artery, and subsequent drug-eluting balloon angioplasty due to restenosis. At the last procedure, the right external iliac artery was stented.

Angioplasty

CAS was performed through brachial approach in the second case and through a femoral approach in the other cases. The left ICA was engaged in a telescopic fashion with a triple coaxial system formed by a 6-F Accuflex sheath (Bipore Medical Devices Inc., Northvale, NJ, USA) and a preloaded 5-F, 125-cm diagnostic catheter (MP, Bern) over a 0.035-inch soft hydrophilic guidewire (Terumo, Tokyo, Japan). Under distal embolic protection [EPI FilterWire EZ (Boston Scientific) or SpiderFX (ev3, Plymouth, MN, USA)], the in-stent lesion was predilated using a 3.5×20-mm coronary balloon (Maverick; Boston Scientific) and then treated with two 1-minute inflations of a 4×40-mm paclitaxel-eluting balloon (Amphirion In.Pact; Medtronic CardioVascular, Santa Rosa, CA, USA). A 3-month course of dual antiplatelet therapy was prescribed.

Outcomes

All patients were asymptomatic at their latest clinical follow-up at 12, 22, and 36 months, respectively. The ICA stents were patent, with normal PSVs, at 6, 12, and 24 months, respectively. Carotid angiography (Fig. 3) at 6 months in patient 3 showed a widely patent stent.

DISCUSSION

CAS is a valid alternative to CEA, with high procedural safety and efficacy; the best choice for an individual patient, however, is still debated, as CAS seems to carry a higher risk of periprocedural stroke, while CEA might be

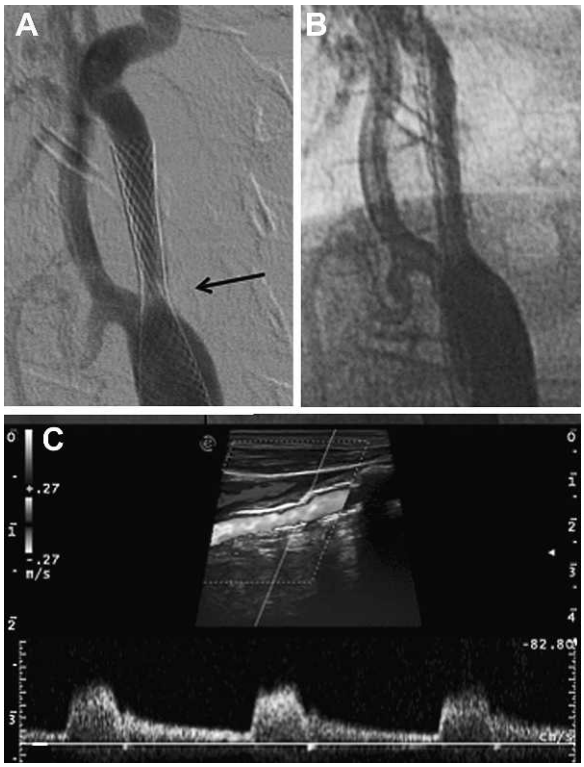

Figure 2 ◆ (**A**) Digital subtraction angiogram of the left ICA in a 70-year-old woman showing critical restenosis (arrow). (**B**) Final angiographic result (arrow) after inflation of a paclitaxel-eluting balloon under distal embolic protection. (**C**) The 12-month duplex examination showing an optimal result.

associated with higher rates of myocardial infarction.[6] The long-term durability of both CAS and CEA, however, can be undermined by the occurrence of restenosis, in particular after stenting.

Different patterns of in-stent restenosis may have important prognostic implications.[7] Possible management options for carotid ISR include medical treatment (“watchful waiting”), repeat balloon (or cutting balloon) angioplasty, re-stenting, or a surgical approach (CEA with stent removal, carotid artery bypass, or interposition graft).[5] As yet, though, there is no ideal approach, and the therapeutic decision is taken on a case-by-case basis. Balloon angioplasty and re-stenting can be performed with a low incidence of periprocedural complications, but rates of recurrent ISR, both early and (mainly) late, remain high.[3]

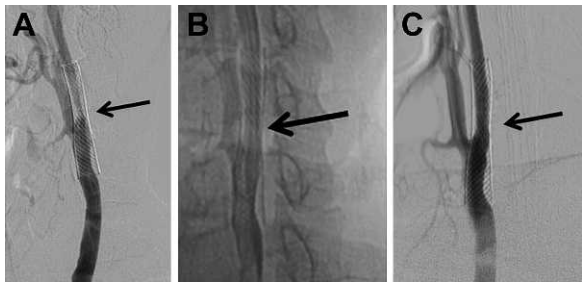

Figure 3 ◆ (**A**) Baseline digital subtraction angiogram of a left internal carotid artery with evidence of severe restenosis (arrow). (**B**) Final digital subtraction angiogram after paclitaxel-eluting balloon dilation. (**C**) Six-month follow-up carotid angiography showing continued stent patency (arrow).

In our cases, we used an alternative therapeutic option, the DEB, which was originally designed to overcome the limitations of drug-eluting stents in the coronary field, including late stent thrombosis, recurrent restenosis, and strong dependency on prolonged dual antiplatelet therapy.[8] Significant advantages of DEBs include fast, homogeneous release of a high dose of drug and absence of a permanent foreign body and polymeric material. Potential limitations of DEBs are the acute elastic recoil typical of balloon angioplasty and the variability of pharmacokinetics.[9] Paclitaxel is the primary drug for DEB technology because of its potent antiproliferative effect and prolonged tissue retention.[10]

There are 3 main types of DEB technologies, all of which have a 3-$\mu g/mm^2$ concentration of paclitaxel in proprietary matrices on the balloon surface. In the Paccocath, the paclitaxel is embedded in a hydrophilic iopromide spacer, and the porous coating together with the high contact surface increases solubility and elution of the drug. However, with this technology, up to 15% of the initial dose of the drug at best is delivered to the vessel wall during a 60-second inflation.[11] Medtronic’s In.Pact system has a natural coating that reduces the total drug elution time to 30 to 60 seconds; the majority of the drug is released within the first 30 seconds. The total drug load depends on both size and length of the balloon.[8] The second generation of Eurocor’s Dior incorporates a natural hydrophilic

resin; two 20-second inflations each release 35% of the drug.[8]

DEB technology has been proven effective for the treatment of both coronary and peripheral ISR. In the PACCOCATH ISR I trial,[12] for example, late lumen loss was 0.03 mm vs. 0.74 mm (p=0.002) for conventional angioplasty. DEB also was clinically effective in the treatment of de novo and restenotic peripheral lesions,[13] but data are limited on their use in the neurovasculature. In a small registry enrolling 51 patients with intracranial ISR, Vajda et al.[14] showed better midterm results for DEB vs. angioplasty in terms of recurring restenosis (9% vs. 50%). Of note, in 4 cases, a coronary DEB could not be navigated through the in-stent restenotic lesion.

In our patients, technical success was achieved using a simple, stepwise telescopic technique[15] without complications, and midterm follow-up appears encouraging. All lesions were predilated with a conventional balloon, followed by prolonged inflation of the DEB, as recommended for optimal drug delivery.[8] Although macroscopic debris was not found in the filters, cerebral protection is still needed in treating ISR with DEBs. It should also be noted that proximal protection devices cannot be used in ISR, as the external carotid artery is always covered by stent struts.

Another important point concerns the available DEB sizes: we used 0.014-inch–compatible coronary balloons, which limited our largest available size to 4.0 mm. DEBs measuring 5.0 or 6.0 mm in diameter are available on 0.018-inch or 0.035-inch platforms, and their use could potentially increase the complexity of the procedure. Moreover, as the main point of DEBs is not to maximize the lumen but to release the drug in a narrowed area that rarely exceeds 4 mm in diameter, we believe that the 4.0-mm balloon (which can be inflated up to 14 to 16 atmospheres) might be suitable for many cases. A good compromise, however, could be the availability of a 5.0-mm DEB compatible with a 0.014-inch wire.

Interventionists should be aware of this emerging therapeutic strategy because DEBs could potentially represent a balanced, attractive solution for carotid ISR, in which avoiding the disadvantages a permanent polymeric implant is particularly attractive. DEBs might be useful mainly to treat diffuse, proliferative (type 4) restenosis, while a potential use for predilation of long, calcified lesions (at high risk of stent fracture and restenosis) could be anticipated. Additionally, the possibility of routine predilation with DEB in the restenosis-prone intracranial circulation must be considered. However, some questions still remain, especially regarding drug delivery to the vessel wall or the best option in event of suboptimal DEB angioplasty.

Conclusion

DEBs are an emerging strategy for carotid ISR, with encouraging midterm results in these initial patients. However, they must be confirmed by larger studies, possibly involving new, dedicated neurovascular devices able to navigate in tortuous supra-aortic and intracranial vasculature.

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